Peer Review File

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Reviewer A

A few comments:

It is unclear how many patients were enrolled in this trial. The abstract and Table 1 mention 36 patients, while the results section mentions 32 patients. Please clarify this discrepancy.

In the results section of the abstract, please rephrase the sentence to differentiate between systemic and intracranial progression-free survival (PFS).

Please correct the percentage of metastatic sites other than CNS in Table 1.

Please consider adding an additional table describing the molecular profiling of the patients, including information on KRAS, STK11, KEAP, and others.

Please expand the discussion on the tolerability and importance of brain irradiation, as it demonstrates impressive outcomes compared to unirradiated patients.

Please add a section describing the limitations of the study, including the small number of participants.

From my point of view, this manuscript can be considered for publication after addressing the comments.

Responses to Reviewer A

Comment 1: It is unclear how many patients were enrolled in this trial. The abstract and Table 1 mention 36 patients, while the results section mentions 32 patients. Please clarify this discrepancy.

Reply 1: We greatly appreciate your comments. A total of 36 patients were enrolled in this trial and received at least one dose of treatment. These patients constituted the full analysis set and safety set in the study. While a total of 32 patients had at least one post-treatment tumor assessment and were included in the RECIST1.1 efficacy analysis set. Based on your comments, we clarified these definitions in the Results section. Detailed changes are listed below.

Changes in the text: Results-Patients (Page 9, Line 2): "A total of 36 patients were eligible and treated with at least one cycle of treatment (safety set, Supplementary Figure 1)."

Results-systemic efficacy (Page 9, Line 12): "A total of 32 patients had at least one post-treatment tumor assessment and were included in the RECIST1.1 EAS."

Results-intracranial efficacy (Page 10, Line 9): "A total of 30 patients had at least one post-treatment intracranial tumor assessment and were included in the RANO-BM EAS."

Comment 2: In the results section of the abstract, please rephrase the sentence to differentiate between systemic and intracranial progression-free survival (PFS).

Reply 2: Thank you for your kind suggestion. We have rephrased the sentences in the Abstract-Results section based on your comments. Detailed changed are listed below.

Changes in the text: Abstract-Results (Page 3, Line 19): "One-year systematic PFS rate and One-year intracranial PFS rate was 36.8% and 55.8%, respectively."

Abstract-Results (Page 4, Line 3): "while alterations in cytokine receptors pathway predicted higher intracranial ORR (P=0.081), prolonged systematic PFS (HR=0.16, P=0.021) and OS (HR=0.71, P=0.029)."

Comment 3: Please correct the percentage of metastatic sites other than CNS in Table 1.
Reply 3: Thank you for pointing out this issue. We have corrected this mistake in Table 1 (please see Table 1-R1).
Changes in the text: Table 1-R1: "Metastatic sites other than CNS: None=6 (16.7)"

Comment 4: Please consider adding an additional table describing the molecular profiling of the patients, including information on KRAS, STK11, KEAP, and others.
Reply 4: Thank you for your suggestion. Indeed, mutations in KRAS, STK11 and KEAP are reported to potentially affect the efficacy of immunotherapy. Genomic analysis with a next-generation sequencing panel of 425 genes was performed on tumor tissues from 13 patients. KRAS mutations were detected in three patients, while no mutation in STK11 and KEAP was detected. Molecular profiling results of these patients are listed in Supplementary Figure 4.
Change in the text: Results-Biomarker analysis (Page 11, Line 21): "Molecular profiling results of these patients are listed in Supplementary Figure 4."

Comment 5: Please expand the discussion on the tolerability and importance of brain irradiation, as it demonstrates impressive outcomes compared to unirradiated patients.
Reply 5: Based on your suggestion, we have expanded Paragraph 4 in the Discussion to discuss the importance and tolerability of brain radiotherapy for patients with brain metastases. Detailed changes are listed below.
Changes in the text: Discussion-Paragraph 4 (Page 14, Line 14): "Brain radiotherapy remains a crucial therapeutic strategy for patients with brain metastases. Recent progress in stereotactic techniques and radiotherapy equipment has provided greater efficacy and better tolerability for patients subjected to brain radiation. Despite the wide application of immunotherapy in advanced NSCLC and the high occurrence of brain metastases in this population, data on the relationship between immunotherapy and brain radiotherapy are scarce. Evidence from retrospective studies suggest that the combination of brain radiotherapy and systemic immunotherapy is superior to radiotherapy alone in terms of local disease control and overall survival[22-24]. Results from the current study further indicate that systemic immunotherapy administered concurrently with or shortly following brain radiotherapy could provide more durable disease control and survival benefits for patients with BM. Nevertheless, the favorable outcomes observed with irradiated patients in this study might be confounded by the fact that patients with oligometastatic brain diseases were more likely to receive prior brain radiotherapy. Meanwhile, whether the short interval between brain radiation and systemic treatment contribute to the efficacy observed in this study is also unknown. Future studies are warranted to validate our findings and to further investigate the relationship, sequence and combination of local radiotherapy and systemic immunotherapy in advanced NSCLC with brain metastases."

Comment 6: Please add a section describing the limitations of the study, including the small number of participants.
Reply 6: Thank you for your comments. Accordingly, we added a section at the end of the Discussion to specifically discuss limitations in the current study (please see Page 16, Line 6).

Changes in the text: Discussion-Limitations (Page 16, Line 6): "Limitations of the current trial included its single-arm nature and small sample size. Additionally, only one third of patients provided tumor tissues for biomarker analysis, which could limit the power of our biomarker exploration. Meanwhile, this study recruited patients solely from China, which may undermine the representativeness of the study population. However, given that previous pivotal trials on immunochemotherapy reporting similar results in Asian and Western patients, we assume that results of our study could be extrapolated to Western patients."

Reviewer B

This is an interesting single-arm phase II study designed to evaluate the intracranial response pattern, tolerability and biomarkers of tislelizumab plus chemotherapy in NSCLC with untreated, symptomatic or recently-irradiated brain metastases. The study is of importance because prospective data on the intracranial efficacy and tolerability of immunotherapy in patients with concurrently- or recently-irradiated BM are very limited.

In general, the study was satisfactorily designed and its outcome was adequately presented. The major limitation of this research was very low number of patients who provided tumor tissues for biomarker analysis (only 13 individuals). This limitation, however, was addressed in a discussion. While the outcome of this trial is of clinical importance and the biomarker studies are of potential future interest I suggest to address following issues in corrected version of the manuscript:

1) It was observed that patients with prior brain radiotherapy trended towards higher systemic (83.3% vs 34.6%) and intracranial ORR (75.0% vs 42.3%). Most of irradiated patients (6 out of 7) had stereotactic treatment. It may suggest that mostly the patients with oligometastatic brain disease were selected for brain radiotherapy, hence the difference in response rates may be attributed not only to the effect of radiotherapy but also to oligometastatic nature of the brain disease. Please consider a comment on this issue

2) Line 94: use past tense: were allowed

3) Line 139 this is a single arm study. Why do you calculate a number of patients needed to provide a single-sided significance level of 0.05 with 80% power? It seems quite inappropriate in a single arm study. The two groups comparisons presented do not refer to randomized data, also the number of patients in two groups are not the same so the calculation provided seems invalid.

4) Line 173 "The primary endpoint of the 174 trial was met" Such statement seems inappropriate because the expected 1-year PFS that would delineate effectiveness or futility of therapy was not pre-defined. You met, however, the adequate follow-up period that allowed to calculate 1-year PFS.

5) One of the most interesting outcomes of the study was finding that patients with alterations in cytokine receptors pathway had higher likelihood of intracranial response and significantly longer PFS. Please confided expanding description of what alterations were investigated and which of them were of prognostic importance.

Responses to Reviewer B

Comment 1: It was observed that patients with prior brain radiotherapy trended towards higher

systemic (83.3% vs 34.6%) and intracranial ORR (75.0% vs 42.3%). Most of irradiated patients (6 out of 7) had stereotactic treatment. It may suggest that mostly the patients with oligometastatic brain disease were selected for brain radiotherapy, hence the difference in response rates may be attributed not only to the effect of radiotherapy but also to oligometastatic nature of the brain disease. Please consider a comment on this issue.

Reply 1: Indeed, the better efficacy observed with irradiated patients in this study might be confounded by the fact that patients with oligometastatic brain diseases were more likely to receive prior brain radiotherapy. Based on your suggestion, we revised Paragraph 4 in the Discussion to add related comments on this issue (please see Page 15, Line 1).

Changes in the text: Discussion-Paragraph 4 (Page 15, Line 1): "Nevertheless, the favorable outcomes observed with irradiated patients in this study might be confounded by the fact that patients with oligometastatic brain diseases were more likely to receive prior brain radiotherapy. Meanwhile, whether the short interval between brain radiation and systemic treatment contribute to the efficacy observed in this study is also unknown. Future studies are warranted to validate our findings and to further investigate the relationship, sequence and combination of local radiotherapy and systemic immunotherapy in advanced NSCLC with brain metastases."

Comment 2: Line 94: use past tense: were allowed.

Reply 2: We have corrected the tense based on your comments.

Changes in the text: Methods-Study design and patients (Page 6, Line 8): "… antiepileptics or dehydration treatments (clinically stable) were allowed."

Comment 3: Line 139 this is a single arm study. Why do you calculate a number of patients needed to provide a single-sided significance level of 0.05 with 80% power? It seems quite inappropriate in a single arm study. The two groups comparisons presented do not refer to randomized data, also the number of patients in two groups are not the same so the calculation provided seems invalid.

Reply 3: Thank you for pointing out this problem for us. Since this is a single-arm phase II study, we set the estimated enrollment number to allow preliminary evaluation of safety and efficacy. Based on your comments, we revised the related statement in the manuscript (please see Page 8, Line 5).

Changes in the text: Methods-Statistical analysis (Page 8, Line 5): "The estimated number of enrollment for this study was 35 to allow preliminary evaluation of efficacy and tolerability."

Comment 4: Line 173 "The primary endpoint of the trial was met" Such statement seems inappropriate because the expected 1-year PFS that would delineate effectiveness or futility of therapy was not pre-defined. You met, however, the adequate follow-up period that allowed to calculate 1-year PFS.

Reply 4: We appreciated your comments. The original statement is indeed inappropriate in the context of the current study. Therefore, we revised the statement in Results based on your suggestion (please see Page 9, Line 18).

Changes in the text: Results-Systemic efficacy (Page 9, Line 18): "With a median follow-up duration of 12.8 months, 1-year PFS rate in the RECIST1.1 EAS was 36.8% (95%CI, 18.0-55.7)."

Comment 5: One of the most interesting outcomes of the study was finding that patients with alterations in cytokine receptors pathway had higher likelihood of intracranial response and significantly longer PFS. Please confided expanding description of what alterations were investigated and which of them were of prognostic importance.

Reply 5: Thank you for your suggestion. Based on your comments, we added specific alterations in the cytokine receptors pathway in Results (please see Page 12, Line 10). However, given that only 13 patients provided tumor tissues for biomarker analysis, we were not able to determine which alterations among them were of prognostic importance. This is a limitation of the current study. More studies are warranted to further investigate this issue.

Changes in the text: Results-Biomarker analysis (Page 12, Line 10): "Patients with alterations in cytokine receptors pathway (CYSLTR2, KDR, EGFR, FLT1, PGR, IL7R) had higher likelihood of intracranial response (P=0.081, Fig 3A) and significantly longer systematic PFS (HR=0.16, 95%CI=0.03-0.92, P=0.020, Fig 3B) than patients without."